How a Damaged Blood Vessel Wall Contributes to Thrombosis and Hypertension

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Key Words

Endothelial cell · Hypertension · von Willebrand factor
Thrombosis · Virchow's triad

Abstract

In order to maintain an anticoagulant nature, the healthy endothelium secretes factors such as tissue plasminogen activator, ADPase, and expresses membrane thrombomodulin. However, when damaged, it releases increased amounts of pro-coagulants such as von Willebrand factor. Similarly, the healthy endothelium uses nitric oxide, prostacyclin and other molecules to help maintain normal blood pressure, and these molecules also inhibit platelet activity. But a dysfunctional endothelium fails to produce these vasodilators so that vasospasm and hypertension can result. Thus the (damaged/dysfunctional) endothelium can contribute to Virchow's triad by failing to maintain an anticoagulant surface and in failing to correctly regulate blood pressure, factors that are likely to promote thrombosis and hypertension.

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Introduction

Virchow's triad considers three aspects of the pathophysiology of thrombosis, one being the blood vessel wall. The entire blood vessel consists of a number of layers of different cells and tissues, each performing different functions in different arteries, capillaries and veins. Large arteries are typified by an outermost layer of smaller arterioles and venules (the adventitia) that provide nutrient, and connective tissue components to provide support and anchorage. The middle layer (media) is composed mostly of smooth muscle cells (that provide vascular tone) with a small number of fibroblasts. The innermost layer of these cells, the intima, is that which interfaces directly with the blood, is composed entirely of endothelial cells sitting on a basement membrane that separates it from the media. These endothelial cells do not merely form a passive layer between the blood and the rest of the blood vessel, but perform vital functions in haemostasis, managing tissue fluid and leukocyte movement into the vessel wall, and in regulating vascular tone [1]. It follows that damage to the endothelium by any one of a number of pathophysiological processes, leading to dysfunction, will result in many adverse changes, most of which promote thrombosis, oedema and hypertension. However, the precise mechanisms by which the endothelium justifies its position in Virchow's triad are only now becoming apparent. Broadly speaking, these areas of pathophysiology include thrombosis and haemostasis, and hypertension.

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1424-8832/04/0336-0445\$21.0/0

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Haemostasis and Thrombosis

A healthy endothelium provides an anti-coagulant and anti-platelet surface with the presence of certain cell surface glycoproteins and the release of various molecules, some of which are stored pre-formed in specialised and unique Weibel-Palade bodies [1-3]. Examples of the former glycoproteins include thrombomodulin, tissue factor and ectonucleotidase(s) that act, respectively, as a receptor for thrombin, as an initiator of coagulation by its interaction with coagulation factor VII, and to minimise the pro-thrombotic effects of nucleotides such as ADP (table 1). However, various pathological processes (such as oxidants or protease digestion) can cause the cleavage or shedding of these molecules from the cell surface so that a soluble form that can be measured by ELISA appears in the blood. Thus one of the features of a damaged or dysfunctional endothelium is increased plasma levels of various molecules normally present as part of the cell membrane. The question therefore is whether or not the appearance of these molecules in the plasma, such as soluble thrombomodulin, reflect a loss of the cell membrane form. As membrane thrombomodulin is essentially anti-coagulant, then its loss from the cell surface may tip haemostasis towards pro-coagulation [4,5]. A further question is whether or not these soluble forms are still biologically active. Similarly, tissue factor is pro-coagulant, and therefore tissue factor pathway inhibitor is obviously anti-coagulant. The consequences for thrombosis of increased plasma levels of both in, for example, peripheral artery disease, are therefore unclear [6]. Nevertheless, since increased levels of all the plasma forms of cell surface molecules are found in atherothrombotic disease, it may be presumed that they do indeed reflect a shift towards thrombosis. However, the picture is further compounded by the fact that some molecules, such as tissue factor, are present on non-endothelial cells such as monocytes/macrophages [7].

The endothelium also secretes/releases a variety of molecules that may be active in thrombosis and haemostasis. Foremost among these is von Willebrand factor, high levels of which have been repeatedly shown to predict major cardiovascular events [8-11]. However, this may be because such high levels reflect endothelial perturbation and/or the promotion of thrombosis. The latter is possible as von Willebrand factor has the capacity to cross-link platelets via glycoprotein-1b and mediate their adhesion to components of the sub-endothelium such as collagen. Increased endothelial tissue plasminogen activator is also a predictor of adverse cardiovascular events, but, again, its role in thrombosis and fibrinolysis is clouded by changes in levels of its regulator, plasminogen activator inhibitor, that may also be

produced by platelets and other cells [8,11,12]. Nonetheless, increased levels of these molecules are present in thrombotic disease and many of its risk factors, although it is again unclear whether or not these molecules have a direct and primary effect on haemostasis or are merely markers of severe disease although the former is clearly attractive.

Table 1. Endothelial molecules important in thrombosis and haemostasis, and hypertension.

Important in thrombosis and haemostasis

Cell surface molecules:	Thrombomodulin Heparin Protein C receptor Tissue factor Ectonucleotidase
Secreted/released molecules:	Tissue factor pathway inhibitor Tissue plasminogen activator von Willebrand factor (vWf) Factor V Protein S Plasminogen activator inhibitor Prostacyclin Nitric oxide Thromboxane Platelet activating factor

Important in hypertension

Nitric oxide
Angiotensin I and II
Bradykinin
Endothelin
Prostacyclin
Thromboxane A2
Prostaglandin H2
Serotonin
Histamine
Substance P

n. b. Some molecules are present in both categories and many are not specific for the endothelium.

Hypertension

The fact that atherosclerosis is a disease anatomically specific for arteries (at high blood pressure) compared to veins (at low blood pressure), despite no essential difference in blood cholesterol, glucose, and the products of cigarette smoking between these vessels, underlines the importance of this risk factor. Correct vascular tone is regulated by a balance of endothelial-derived vasodilators (such as nitric oxide and prostacyclin), and vasoconstrictors (such as endothelin and angiotensin) that act on the smooth muscle

cells of the media (table 1). Indeed, entire classes of successful anti-hypertensive agents are directed towards these molecules (e.g. angiotensin converting enzyme inhibitors and angiotensin receptor blockers) whilst another is well into the development process (i.e. endothelin antagonists).

Biochemical evidence of the importance of the endothelium in regulating blood pressure has been present for over 20 years with discovery of endothelium-derived relaxing factor in an animal in-vitro model, a property subsequently shown to be due to nitric oxide [13]. All the major risk factors for atherosclerosis have been associated with impaired nitric oxide activity. However, although a paradigm for active damage to the endothelium by a precise agent, for example, oxidized LDL-cholesterol, is attractive, failure to synthesise nitric oxide may simply be due to lack of its metabolic substrate, L-arginine. Thus hypertension, and probably atherosclerosis, may follow from the inability of the endothelium to produce sufficient amount of this molecule to permit vasodilation [14,15]. Increased blood flow and turbulence in hypertension may also lead to alterations in shear forces. This is suggested by the observation of decreased vasodilator function at coronary artery branch points that have a predilection for atherosclerosis [1,16]. Interestingly, Luscher has debated whether or not the endothelium in hypertension is a bystander, a target, or a mediator [17].

Participation in Both Processes

A fault with this developing discussion is the placement of arbitrary barriers between different pathophysiological processes, an approach that fails to emphasise the double life of some molecules, e.g. platelet activating factor is also a vasoconstrictor. Similarly, nitric oxide does not only regulate blood pressure but also has a role in inhibiting platelet function (adhesion, activation, aggregation and secretion). Prostacyclin, which does not affect platelet adhesion, acts synergistically with nitric oxide to inhibit other steps in the platelet activation cascade [1]. It follows, therefore, that endothelial damage leading to reduced levels of these molecules, may also, at least in theory, have pro-thrombotic repercussions. However, again, the picture is far from clear

as angiotensin II from the endothelium not only has vasoconstrictor activity but is also pro-thrombotic. Thus if we presume that a damaged endothelium fails to release vasoactive mediators (such as nitric oxide) that would lead to hypertension, then it would also fail to release angiotensins that would normally promote hypertension and thrombosis [18].

Although many substances, including thrombin, cause the slow release of endothelin from endothelial cells in vitro, any in vivo effects are unclear [19]. Additionally, there is evidence that bradykinin has a role in fibrinolysis, and activation of the renin-angiotensin system can also disturb the balance of fibrinolysis by stimulating excess production of plasminogen activator inhibitor [20]. Similarly, hypertensive patients seem likely to have increased tissue plasminogen activator and plasminogen activator inhibitor that may be the result of a damaged endothelium [21]. A final point leading to difficulty is that hypertension can be associated with an increased risk of thrombosis independently of the endothelium, i.e. raised fibrinogen, a molecule produced mainly by the liver, and abnormalities in blood platelets [22-23]. This illustrates the complexity of vascular biology and medicine.

Conclusions

Damage to the endothelium can contribute to Virchow's triad in two major areas. Hypertension may follow from loss of the regulation of vascular tone and the balance between, for example, nitric oxide and endothelin. Thrombosis is likely to be promoted by a damaged endothelium that releases high levels of prothrombotic von Willebrand factor and has lost anticoagulant membrane thrombomodulin. There are also numerous examples of molecules (e.g. thromboxane, angiotensin and platelet activating factor) that may participate in both pathological processes. However, the extent to which these directly or indirectly participate in Virchow's triad, or are simply marking disease, is unclear. Nevertheless, the successful treatment of the risk of thrombosis with aspirin strongly implicates the platelet, a cell profoundly influenced by the endothelium.

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